Annals of Surgical Oncology 15(4):986–992
DOI: 10.1245/s10434-007-9731-y

Selection for Resection of Hepatocellular Carcinoma and Surgical Strategy: Indications for Resection, Evaluation of Liver Function, Portal Vein Embolization, and Resection

Dario Ribero, MD,[1] Steven A. Curley, MD,[1] Hiroshi Imamura, MD,[2] David C. Madoff, MD,[3] David M. Nagorney, MD,[4] Kelvin K. Ng, MD, PhD,[5] Matteo Donadon, MD,[6] Valerie Vilgrain, MD,[7] Guido Torzilli, MD, PhD,[6] Mark Roh, MD,[8] and Jean-Nicolas Vauthey, MD[1]

[1]Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, Texas 77030-4009, USA
[2]Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan
[3]Department of Interventional Radiology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, Texas 77030-4009, USA
[4]Division of Gastroenterologic and General Surgery, Mayo Clinic, RochesterMinnesota, USA
[5]Department of Surgery, The University of Hong Kong, Medical, Centre Queen Mary Hospital, Hong Kong, China
[6]Liver Surgery Unit, Third Department of Surgery, University School of Medicine, Istituto Clinico Humanitas IRCCS, Rozzano, Milan, Italy
[7]Department of Radiology, Hôpital Beaujon, Clichy, France
[8]Department of Surgery, Drexel University College of Medicine, Allegheny General Hospital, Pittsburgh, Pennsylvania, USA

Key Words: Hepatocellular carcinoma–Liver resection—Patients selection—Portal vein embolization—Chemoembolization—Intraoperative ultrasonography—Radiofrequency ablation.

Among the potentially curative treatment options for hepatocellular carcinoma (HCC), liver resection is widely considered the mainstay of curative therapy. An important aspect of the morbidity, mortality, and long-term outcome of liver resection for HCC relates to patient selection. Choice of treatment primarily depends on tumor stage and the functional status of the liver because most patients with HCC harbor chronic liver disease.[1] For this reason, when compared with percutaneous ablation therapies or transarterial chemoembolization (TACE), surgery has a higher risk as a result of removal of functioning liver parenchyma. Careful assessment of the clinical severity of cirrhosis and the liver functional reserve is therefore pivotal to ensure suitable selection of appropriate candidates for resection.

Our objective is to review the current indications for liver resection in patients with HCC, to present the current criteria for selection of surgical candidates, and to discuss preoperative and intraoperative strategies to improve the safety of liver resection.

TUMOR STAGE

The assessment of tumor extent is the primary step for determining resectability and the appropriate type of surgical resection. Triphasic contrast-enhanced computed tomography (CT) is essential to define the number and size of the HCCs; to detect the presence of satellite nodules and tumor invasion of the portal vein, its branches, or the inferior vena cava; to ex-

Received June 11, 2007; accepted July 17, 2007; published online January 31, 2008.
Address correspondence and reprint requests to: Jean-Nicolas Vauthey, MD; E-mail: jvauthey@mdanderson.org

clude any extrahepatic metastasis; and, for surgical planning, to clarify the relationship of the tumors with the intrahepatic vascular and biliary structures. Magnetic resonance imaging is the imaging modality of choice when contrast agents are contraindicated or better lesion characterization is needed. The role of positron emission tomography in the preoperative workup is still not standardized, but it can be useful to detect extrahepatic metastases.

Because most HCCs develop in patients with chronic liver disease due to hepatitis virus infection or alcohol abuse,[1] the prognosis of HCC patients depends not only on tumor stage, but also on the underlying liver function. Therefore, several prognostic staging models,[2] accounting for both the extent of HCC and the functional reserve of the liver, have been developed to predict survival and assess outcomes of therapy. One of these systems, from the Barcelona Clinic Liver Cancer (BCLC) group, stratifies patients into four categories (i.e., early, intermediate, advanced, and terminal), recommending for each disease stage different treatment options.[3] According to the BCLC staging system, which has been recently integrated into the American Association for the Study of the Liver (AASLD) guidelines,[4] hepatic resection has a marginal role in the treatment of HCC and is indicated only in patients with early-stage HCC defined empirically by (1) the Milan criteria[5] (and not by the tumor, node, metastasis system American Joint Committee on Cancer/International Union Against Cancer staging systems)[6,7]; (2) normal clinical performance status; and (3) preserved liver function (bilirubin levels <1 mg/dL, absence of portal hypertension, and Child-Pugh class A status).

There is no doubt that patients with early, small HCC have excellent prognosis after hepatic resection.[8] However, retrospective analyses of large-size surgical series show that 43% to 48% of patients treated with curative liver resection have disease classified as being in the intermediate or advanced stages according to the BCLC flowchart.[9,10] Nonetheless, in such patients, liver resection yields favourable survival outcomes, with 3- and 5-year survival estimates up to 78% and 39%, respectively.[9,10] It must also be noted that selection of patients for liver resection purely on the basis of any clinical HCC staging system does not account for comorbidity and anatomic factors such as the site of the HCC and the characteristics of the hepatic segment harboring the tumor, whether atrophic or hypertrophic. Indeed, a large pedunculated HCC in an atrophic hepatic segment may be resected with minimal adjacent functional liver, whereas a small HCC centrally located in a hypertrophic lobe would require resection of most of the functional liver.

Taking into consideration the outcome data reported from Eastern and Western centers[6,9,11–14] and the limitations imposed by the rigidity of any selection scheme, the indications for liver resection in patients with HCC can be summarized as follows. On the basis of preoperative imaging, hepatic resection is nowadays considered to be feasible when all tumor nodules can be technically excised with negative margins while maintaining an adequately functioning hepatic remnant, when the clinical performance status is $>50\%$ to 60% and systemic comorbidity is compensated. Extrahepatic disease, tumor thrombus in the inferior vena cava, and involvement of the common hepatic artery and portal vein trunk should be regarded as formal contraindications for resection.

EVALUATION OF LIVER FUNCTION

The definition of resectability accounts for both the anatomic issue (i.e., technically feasible resection) and the functional one (i.e., "a resection leaving an adequately functioning hepatic remnant"). An accurate evaluation of the liver functional reserve is therefore crucial to avoid postoperative hepatic insufficiency and mortality.

Currently, in patients with overt cirrhosis, hepatic resection is recommended by the European Association for the Study of the Liver[15] and AASLD[4] only in the setting of preserved liver function. The Child-Pugh classification, which was originally developed to estimate the risk of patients with cirrhosis undergoing operations for portal hypertension, is the oldest and most widely used measure used to evaluate the hepatic function and assess operability. However, the Child-Pugh classification provides only a rough estimation of the metabolic activity of the liver stratifying patients in those with compensated (class A) and those with decompensated (classes B and C) cirrhosis. Its most practical value is therefore identifying patients who are not candidates for resection (Child-Pugh classes B and C). Nevertheless, recent series of hepatectomy in Child-Pugh class A patients have reported a wide range of perioperative mortality rates[16–18] due to the heterogeneity of patients with compensated cirrhosis, raising the question whether this class reliably predict postoperative hepatic decompensation or the regenerative response of the remnant.

In Eastern countries, more sophisticated quantitative liver function tests have been used to further refine patient selection. These tests include the indocyanine green (ICG) clearance test[19,20] and the galactose elimination capacity,[21] the former being the more commonly used and validated one. Patient selection by ICG clearance test has greatly reduced the mortality rate—in some centers to zero.[18,22] In patients with cirrhosis, an ICG retention rate at 15 minutes (ICG R15) of 10% to 20% is considered the upper limit for safe major hepatic resection.[20,23] In Western countries, attention has focused on the presence of portal hypertension, which might be underestimated by the Child-Pugh classification. In a prospective study, 15 of 29 Child-Pugh A patients undergoing liver resection for HCC had a hepatic venous pressure gradient (HVPG), an indirect measure of portal hypertension, ≥10 mm Hg, and 11 of them developed unresolved hepatic decompensation.[24] In addition, a HVPG of < 10 mm Hg was recently found to be associated with a greater 5-year survival than HVPG ≥10 mm Hg (75% vs. 50%, respectively).[25] Measure of HVPG has therefore been advocated a selection factor for resection and has been incorporated into the BCLC system, although further validation of its value is needed.

Because compliance of HVPG measurement is limited, in recent years, clinical surrogates or radiologic signs of portal hypertension, including splenomegaly, abdominal collaterals, thrombocytopenia (platelets < 100,000/mm^3), and esophagogastric varices, have been used to select patients for liver resection.[15] In particular, the prognostic impact of esophageal varices has been evaluated in patients with HCC and cirrhosis. Patients with esophageal varices had a 25% to 28% increased risk of death compared with patients without esophageal varices,[26] which remained an independent predictor of survival regardless of Child-Pugh class, HCC stage, and treatment.

Recently, the Model for End-Stage Liver Disease (MELD) score, which was developed to predict short-term prognosis in patients undergoing transjugular intrahepatic portosystemic shunt and adopted in 2002 by the United Network for Organ Sharing to prioritize organ (liver) allocation, has been shown to predict both morbidity and mortality in patients undergoing liver resection.[16,27] Patients with greater MELD scores (≥9) are at increased risk for postoperative morbidity[27] and 30-day mortality.[16] Similarly, recent studies have demonstrated that MELD scores of < 9 predict both low mortality and reduced morbidity after hepatic resection for HCC.[16] Moreover, if selection for resection combines MELD scores of < 9 and HCC sizes of < 5 cm, 5-year survival reaches 74%.

Another important factor in surgical risk assessment is the presence of underlying hepatitis, which can be inferred from preoperative liver function tests. Serum aspartate transaminase more than twice normal values is predictive of liver failure in patients with cirrhosis after major hepatectomy,[28] and such patients should be regarded as poor surgical candidates. Both in the East and the West, preoperative assessment of the volume of the future liver remnant (FLR) has became an essential evaluation to predict postresection liver status and to select patients for major hepatic resection. With the advancement in accurate assessment of liver function, comorbid illness, which is prevalent in elderly patients, has become a more important factor in predicting the risk of hepatic resection.[29] In a recent study, the presence of comorbidity was the independent factors predictive of perioperative mortality.[30]

FUTURE LIVER REMNANT

Although Child-Pugh classification is useful, ICG clearance and other hepatic reserve tests only estimate the overall hepatic function and do not provide information regarding the FLR, which may vary in size as a result of individual intrahepatic variation or compensatory hypertrophy. Recent studies have emphasized the association between the volume and function of the residual liver after resection.[31–34] Therefore, in patients considered candidates for major hepatectomy, the importance of measuring the FLR is to predict its postoperative function. However, it is still debated to which index the FLR volume should be standardized. Japanese and European authors use the *actual* total liver volume (TLV), defined as the volume of the patient's liver measured directly on CT images minus tumor volume,[32–34] rather than the total *estimated* liver volume, an alternative method by which the total liver volume is calculated by a formula that relies on a linear correlation between TLV and body weight or body surface area in healthy subjects.[35–37]

The concept of total estimated liver volume, originally proposed to estimate the optimal liver mass in transplant recipients, has been applied by North American authors in candidates for hepatic resection and routinely adopted for patient selection for several reasons. First, in countries where obesity affects a high proportion of the population, such a method ensures that the patient's size is properly taken into consideration. Second, in patients with large tumors, such as those frequently observed in the Unites States and in areas with endemic hepatitis B virus, the total volume of the liver is altered.[38] Third, cumulative error rates relative to multiple measurements of individual tumor make the subtractive method less reliable. A recent meta-analysis evaluating the existing formulas for the estimation of the total liver volume in adults indicated the following formula as one of the least biased and most precise: TLV (cm^3) = −794.41 + 1267.28 × body surface area (m^2).[39] In patients who are otherwise candidates for hepatic resection, an inadequate FLR may be the only obstacle to curative resection. In these cases, portal vein embolization (PVE) has been shown safe and effective.

PORTAL VEIN EMBOLIZATION

PVE, by redirecting portal blood flow toward the segments of liver that will remain in situ after surgery, induces atrophy of the embolized segments and compensatory hypertrophy of the FLR.[40] Therefore, PVE can be used to preoperatively increase the volume and improve the function of the FLR and avoid the abrupt increase in the portal venous pressure after liver resection.[41–44] Although normal livers have a better regenerative capacity than do fibrotic or cirrhotic ones, several studies have shown that PVE induces clinically important hypertrophy of the FLR in patients with chronic disease,[33,34] thereby reducing the risk for postoperative hepatic insufficiency and improving the safety and tolerance of major liver resection.[33,34]

The indications for PVE depend on three critical factors: the volume of FLR, the patient's size, and the presence or absence of underlying liver disease, which is a major concern in patients with HCC.[38] These factors must be further considered in the setting of the patient's comorbidities (e.g., diabetes) that may affect hepatic regeneration.[45] For patients with cirrhosis, PVE is indicated when the FLR is ≤40% of TLV.[34,46] In the East, where the ICG R15 is routinely assessed, PVE has been advocated for FLR volumes of ≤40% when the ICG R15 is ≤10%, and for FLR volumes of ≤50% when the ICG R15 is 10% to 20%. In patients with ICG R15 >20%, major liver resections are considered formally contraindicated even after PVE.[32] Contraindications to PVE include tumor invasion of the portal vein to be resected because the portal flow is already diverted, tumor extension to the FLR, uncorrectable coagulopathy, portal hypertension, and renal failure.[43] In patients with biliary obstruction, PVE is contraindicated before drainage of the FLR.

PVE is usually performed percutaneously via either an ipsilateral or a contralateral approach with sonographic and fluoroscopic guidance and with the patient under conscious sedation. Specific technique of PVE procedure in patients with cirrhosis, especially in those with low portal flow velocities, includes selective injection of the embolic material in segmental branches to reduce the risk of embolic agent migration in the FLR; in the presence of large portocaval collaterals, embolization of such collaterals with metallic coils is recommended to increase left hepatic perfusion. Last, because most HCCs are hypervascular tumors fed exclusively by arterial blood flow, some authors propose the combination before surgery of PVE with selective transcatheter arterial embolization[47] or chemoembolization (TACE).[48] This double preparation, with transcatheter arterial embolization or TACE performed 1 to 2 weeks before PVE, aims at preventing tumor progression during the period between PVE and the planned hepatectomy, and at strengthening the effect of PVE by embolizing possible arterioportal shunts, which are frequently observed in cirrhotic livers and HCC tumors. Comparison of results between PVE and sequential TACE and PVE indicates a far higher FLR volume increase, a higher incidence of complete tumor necrosis, and a better 5-year disease-free survival in patients treated with sequential TACE and PVE.[48]

Ten percent to 20% of patients undergoing PVE do not experience adequate hypertrophy of the FLR. This lack of response, which exposes the patients to an increased risk of postoperative liver failure,[34,49] is most probably due to the failure in increasing portal flow to the FLR as a consequence of the presence and/or development of collateral vessels.[34,45,47,50] In the context of patients with chronic liver disease, PVE tests the capacity of the injured liver to regenerate, and the absence of hypertrophy may be considered a contraindication for major hepatectomy.[34,51]

SURGICAL PARENCHYMAL SPARING STRATEGY

In patients with HCC, the goal of the surgical approach is to optimize the oncologic resection (negative margin) while sparing the noncancerous hepatic parenchyma. Intraoperative staging is of the utmost importance because new focal lesions can be detected with intraoperative ultrasonography (IOUS) in approximately 15% to 30% of cases,[52,53] although approximately two-thirds of such new lesions are nonmalignant nodules. The differential diagnosis between regenerative nodules, dysplastic nodules, and early HCCs may be difficult, and the use of contrast-enhanced IOUS may improve the specificity of IOUS and provide information that can affect surgical planning[54] as well as possibly long-term prognosis by decreasing recurrence through the identification of unrecognized multifocal HCC. The surgical strategy is modified on the basis of the findings at IOUS–contrast-enhanced IOUS while keeping the conservativeness of the approach as one of the major goals to achieve along with complete resection. For a conservative approach, the extensive use of IOUS guidance is indispensable. IOUS allows surgeons to minimize the tumor-free resection margins, without the need for a 1-cm safety margin, while achieving negative margin resection.[55–58] This approach, which is also more conservative in complex tumor presentations,[58] may also be associated with a lower expression of growth factors after surgery, which seems related to liver regeneration and tumor recurrence.[59]

Because tumor dissemination from the main HCC is usually through the portal vein branches, in the mid-1980s, Makuuchi et al.[60] proposed that the resected specimen should include at least the segmental or subsegmental portal vein in association with the tumor (anatomic resection). Given the existing wide variations in the anatomy of portal vein branches, IOUS is essential to correctly define the segmental boundaries and to perform a segment-oriented liver resection. The theoretical advantage of anatomic over nonanatomic resection has been demonstrated in two large series in which anatomic resection was found to be an independent factor for both overall and disease-free survival.[11,61] Moreover, tailoring the resection area under IOUS guidance is associated with a mortality and major morbidity approaching zero.[57,58]

Although ablative therapies such as radiofrequency ablation have gained popularity, their efficacy in the treatment of HCC has not been established as equivalent to that of resection or transplantation.[62] Therefore, the role of radiofrequency ablation in the management of HCC should be limited to treat unresectable tumors and as a bridge therapy before liver transplantation.[63,64]

CONCLUSIONS

With careful patient selection, meticulous surgical techniques, and optimal operative care, the current operative mortality of hepatic resection, including major resection for HCC, is $<5\%$. The improved perioperative outcome and long-term survival after resection for HCC have been reported, and these have emphasized the major role of hepatectomy in the treatment of HCC in patients with cirrhosis with preserved liver function (Child-Pugh class A) when complete resection of the tumor can be obtained. In these patients, minor hepatectomy can be safely performed in the presence of normal liver function tests (bilirubin ≤ 1.0 mg%), absence of ascites, and platelet counts of $>100{,}000/mm^3$.[20] Additional criteria for patients considered for major hepatectomy are the absence of clinical portal hypertension, an ICG R15 (if the test is performed) of $<10\%$,[20] and an FLR volume of $\geq 40\%$ of the total liver volume.[32] PVE is indicated in patients with an FLR of $<40\%$ of the total liver volume to induce hypertrophy of the FLR to reduce the morbidity and mortality of major hepatectomy.[34]

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